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Efficacy of High Dose Intravenous Heparin for Treatment of Left Ventricular Thrombi With High Embolic Risk

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Objectives. **This study was performed to assess the efficacy of high dose intravenous heparin to treat mobile or protruding left ventricular thrombi as detected by serial echocardiography.**

Background. **The presence of mobile and protruding left ventricular thrombi greatly increases the risk of arterial embolization, yet optimal therapy, be it thrombolysis, anticoagulation or surgical removal, has not been defined.**

Methods. **Full dose heparin, 31,291 ± 7,980 (mean ± SD) IU/day, to prolong partial thromboplastin time to at least twice normal, was administered intravenously to 23 consecutive patients with 25 mobile and protruding thrombi. Patients were prospectively evaluated for hemorrhagic complications and embolic events during therapy. The presence or absence of thrombi and their size and characteristics were assessed by serial echocardiography.**

Results. **In all 23 patients left ventricular thrombi decreased in size, with disappearance of the high risk features. The duration of high dose heparin infusion was 7 to 22 days (mean 14 ± 4). Thrombus size was reduced from 3.9 ± 2.6 to 0.16 ± 0.38 cm^2, and thrombus disappeared entirely in 19 (83%) of 23 patients. No embolic events were detected during treatment, and the only complication was an upper gastrointestinal hemorrhage that was successfully treated medically.**

Conclusion. **High dose intravenous heparin is a highly effective and safe treatment for completely resolving left ventricular thrombi with high risk features for embolization. Most such thrombi disappear completely within 1 to 3 weeks of this treatment without embolic or hemorrhagic complications.**

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Left ventricular thrombi with mobile or protruding segments seen by echocardiography have been demonstrated to associate with a high risk of arterial embolization (1), with reported incidences ranging from 22% to 100% (2,3). Controversy exists about the best treatment for this condition (4–20). Initial results with urokinase were promising (4), but serious complications during thrombolysis, such as systemic embolization and cerebral bleeding, have been reported more recently (5). Complete resolution of left ventricular thrombi with warfarin over a prolonged period has been reported previously (3,5,7,21). In a retrospective assessment (7), only 2 of 15 thrombi disappeared during 4 months of oral anticoagulant therapy, and other nonrandomized studies showed 50% to 59% complete resolution of left ventricular thrombus with the use of warfarin or low dose heparin for 15 days (21) to 6 to 9 months (3). However, there has been no systematic trial of anticoagulation with the use of a full loading dose of heparin for this condition; therefore, its value remains controversial (3,8,13,14,17,18,20).

In patients with this type of thrombus who were not suitable candidates for thrombolytic therapy or surgical intervention, we have used high-dose heparin empirically with promising results. The present study was therefore undertaken in a series of consecutive patients to evaluate prospectively the efficacy of high dose intravenous heparin for treating mobile or protruding left ventricular thrombi, as assessed by clinical outcome and serial echocardiography.

Methods

Patients. Between January 1990 and July 1993, 23 patients admitted to the University Hospital in Hamburg and Herz-Kreislauf-Klinik in Bevensen had 25 echocardiographically documented left ventricular thrombi that were mobile or protruded into the left ventricular cavity (Table 1). All patients were suitable candidates for anticoagulation (11 women, 12 men; mean [±SD] age 61 ± 12 years, range 36 to 83). Two patients were referred for evaluation of the cardiac source of the embolism, and the remaining patients were referred primarily for evaluation of left ventricular function. The etiologies

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Table 1. Patient Characteristics

Pt No./ Age (yr)	Etiology	Time After MI	WMA	LVEF	Thrombus Location
1/56	CHD	5 yr	Inf, AN	>50%	Basal Inf
2/65	DCM		Global	40%	Apical
3/36	DA (myocarditis)		Global	20%	Apical
4/68	CHD	6 yr	Ant, Sept	40%	Apical
5/70	CHD		Inf, Ant	>50%	Apical
6/67	CHD	Unknown	Ant	>50%	Apical
7/83	CHD	1 mo	Ant, Sept	20%	Apical
8/59	CHD	2 mo	Ant, Sept	40%	Apical
9/53	CHD	30 days	Ant, Sept	20%	Apical
10/71	DCM		Global	40%	Apical
11/63	CHD	3 yr	Global	30%	Apical
12/67	CHD	10 days	Post-Lat, AN	40%	Basal Post
13/70	CHD	2 days	Ant, Lat	>50%	Apical
14/49	CHD	2 yr	Ant, Sept	20%	Apical
15/49	CHD	3 yr	Ant, AN	20%	Apical
16/68	CHD	Unknown	Ant, Sept	20%	Apical
17/74	CHD	Unknown	Ant, Sept	40%	Apical
18/42	Postmyxomectomy		Apical	>50%	Apical
19/46	CHD	1 yr	Ant, AN	40%	Apical
20/78	CHD	Unknown	Ant, Lat, Inf	30%	Apical
21/47	CHD	2 yr	Ant, Lat, Inf	40%	Apical
22/54	CHD	7 yr	Ant, Lat	20%	Ant
23/68	CHD	4 mo	Ant, Lat, Inf	20%	Apical

AN = aneurysm; Ant = anterior wall; CHD = coronary heart disease; DA = drug abuse; DCM = dilated cardiomyopathy; Inf = inferior wall; Lat = lateral wall; LVEF = left ventricular ejection fraction; MI = myocardial infarction; Post = posterior; Pt = patient; Sept = septal wall; WMA = regional wall motion abnormality.

are presented in Table 1. Two patients with coronary disease were taking warfarin >1 year and had prothrombin times between 1.5 and 1.8 times the normal control value at the time of admission; 16 were taking aspirin; and 5 were not receiving anticoagulant or antiplatelet drugs. Two patients with recent myocardial infarction (≤8 days) had received thrombolytic therapy and were receiving low dose subcutaneous heparin (200 IU/kg per day). Global left ventricular ejection fraction and regional wall motion abnormalities are presented in Table 1.

Echocardiography. A commercially available Hewlett-Packard Sonos 1000 and an Acuson 128 XP/10 were used. Transthoracic echocardiography was performed with a 2.5-MHz transducer and recorded on 2/3-in. videotape. Follow-up studies were performed every 2 to 7 days, depending on the clinical course. Mobile or protruding left ventricular thrombus was diagnosed with transthoracic echocardiography in 21 of the patients and with transesophageal echocardiography in the other 3, in whom there was difficulty characterizing the thrombus by transthoracic echocardiography because of inadequate image quality.

Two observers evaluated the echocardiographic recordings independently for overall left ventricular function, regional wall motion abnormalities and the presence or absence of intracavitary thrombus and its morphologic features (size, mobility, protrusion and homogeneity). For the diagnosis of left ventricular thrombus, an echogenic mass had to be seen in at least two orthogonal views, and both had to be distinguishable from adjacent endocardium and associated with a regional wall motion abnormality or global hypokinesia. To be included in this study the thrombus had to be protruding or mobile in multiple views, defined by one of the following criteria: 1) a broad-based protuberant thrombus without a mobile component in 10 patients; 2) a mobile intracavitary thrombus with a narrow stalk in 1 patient; 3) a broad-based mural thrombus with a protruding part and one or more mobile parts in 12 patients. There was a 100% concordance of assessment of echocardiographic protrusion or mobility of the thrombus by two experienced observers (C.C. and S.C.W.H.). Thrombus size was measured from the echocardiographic plane, usually from the apical long-axis or four-chamber view, showing the largest area of thrombus. Follow-up measurements were performed in the same echocardiographic plane as during the baseline recording, as depicted in Figure 1. The mean interobserver variability of the measurement of thrombus size was 0.85 cm^2, and intraobserver variability was 0.45 cm^2.

Heparin therapy. As soon as a protuberant or mobile thrombus was diagnosed, heparin was begun intravenously at a dose of 400 IU/kg per day, adjusted to maintain the partial thromboplastin time at 2.0 to 2.5 times the normal control value (partial thromboplastin time normal range 34 to 58 s). Heparin was stopped when serial echocardiography showed that the thrombus had disappeared echocardiographically or that only a small, flat residual mural thrombus without a mobile or protruding segment was present.

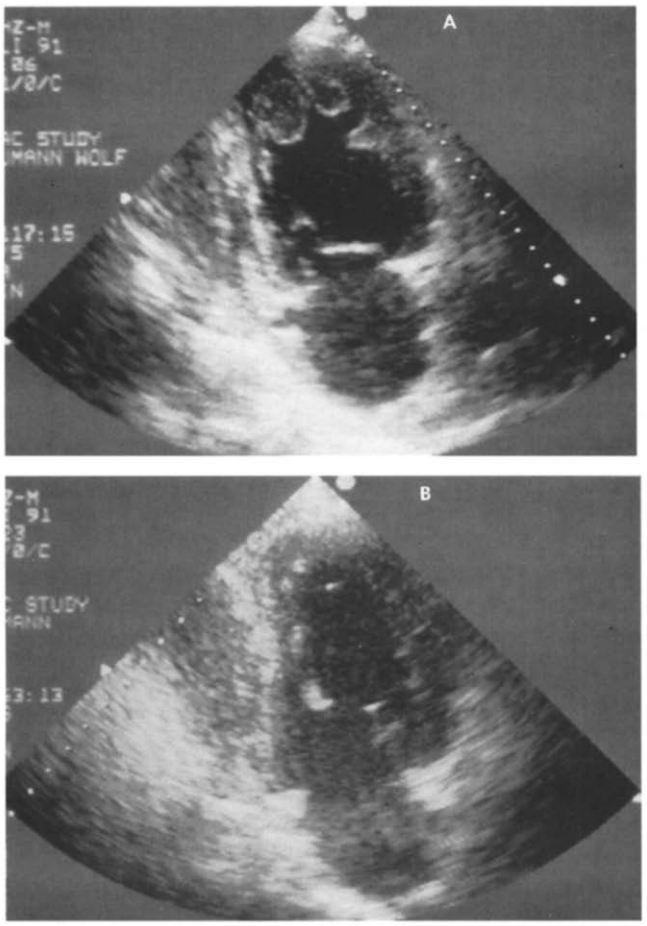

Figure 1. A. Apical long-axis view echocardiogram showing three protruding and mobile thrombi in a drug addict with mild global hypokinesia of a mildly dilated left ventricle. **B.** Two weeks after high dose intravenous heparin administration, all left ventricular thrombi disappeared, both in the same imaging plane and in all other views (not shown).

Statistical analysis. Data are presented as the mean value ± 1 SD. Thrombus size before and after heparin therapy was compared by the Wilcoxon signed-rank test.

Results

During high dose heparin therapy, the size of the left ventricular thrombi decreased from 3.9 ± 2.6 cm^2 (mean ± SD) (range 0.55 to 11.3) to 0.16 ± 0.38 cm^2 (range 0 to 1.5, $p < 0.0001$). Twenty-one of the 25 thrombi in 19 of the 23 patients completely disappeared. The other four thrombi were significantly smaller: Their sizes after heparin therapy were 1.0, 1.5, 0.35 and 0.32 cm^2 (mean 0.8 ± 0.5 cm^2) (Fig. 2). All of the 25 thrombi improved with respect to size or high risk features during high dose heparin therapy. All had lost their mobile component, and only one of them still protruded in one patient. This patient died of abrupt coronary bypass graft occlusion, and an autopsy revealed a small residual left ventricular thrombus consistent with the echocardiographic findings.

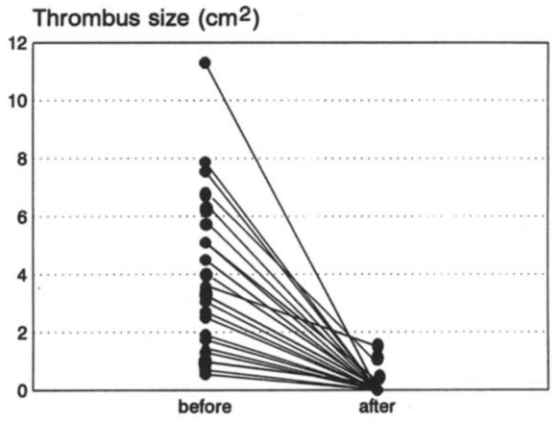

Figure 2. Individual thrombus size assessed by serial two-dimensional echocardiography in all patients before and after high dose intravenous heparin administration.

Two patients experienced embolic events before the initiation of therapy. No emboli were detected during intravenous high dose heparin therapy. The mean dose of heparin was 31,291 ± 7,981 IU/day (range 16,000 to 48,000). The mean partial thromboplastin time was 107 ± 30 s (range 62 to 180). The only serious hemorrhagic episode was an acute upper gastrointestinal hemorrhage that was successfully treated medically without the need for blood transfusion. Minor bleeding complications, such as small hematomas at the injection sites, were observed in eight patients. The mean duration of heparin therapy was 14 ± 4 days (range 7 to 22), depending on when the thrombus disappeared echocardiographically or lost its high risk features.

Patients with left ventricular dilation, reduced left ventricular ejection fraction (<50%) or regional wall motion abnormalities were treated with warfarin after hospital discharge. One patient who was transferred to another hospital after only 4 days of high dose heparin treatment was excluded from the study. He had esophageal carcinoma and a large mobile apical thrombus. The thrombus remained mobile, but its size decreased after 4 days of high dose heparin. The patient was transferred to another hospital, and his heparin regimen was changed to low dose subcutaneous heparin (5,000 IU twice a day). He subsequently had an embolic stroke 7 days after termination of intravenous high dose heparin. Echocardiography revealed a further decrease in thrombus size after this event.

Discussion

This study demonstrates that high dose intravenous heparin is highly effective in completely resolving high risk left ventricular thrombi. The risk of hemorrhagic complications is low in a hospital setting with rigorous control of bleeding variables. Further studies are required to address whether the reduction in embolic risk by rapid resolution of left ventricular thrombus with high dose heparin would be maintained long term by

administration of an oral platelet inhibitor or oral anticoagulant.

Mechanism of action. The mechanism by which heparin can resolve a thrombus is speculative. We hypothesize that high dose intravenous heparin will prevent further deposition of thrombotic material onto the surface of the existing thrombus and that the endogenous thrombolytic system will act on the surface of the thrombus, resulting in endogenous thrombolysis. If endogenous thrombolysis occurs sequentially, reversing the incremental pattern of thrombus formation, new layers of thrombus will be removed first, and older layers will resolve later, preventing dislodgment and embolization. This explanation may account for the absence of embolic events during a sustained period of endogenous thrombolysis.

A low rate of embolic events has also been reported with oral anticoagulant therapy. However, the rate of successful resolution of thrombus is relatively low and varies widely, from 13% to 59% (6,7,11,13,21–23). Why high dose heparin appears to be more effective in resolving left ventricular thrombus than oral anticoagulant is unclear. Rigorous monitoring of anticoagulation in-hospital, with avoidance of subtherapeutic levels, may have contributed to the higher efficacy of high dose heparin compared with oral anticoagulation in an ambulatory setting. Close monitoring over a relatively short period in this study may also have reduced the likelihood of excessive anticoagulation, leading to bleeding complications. There was no embolic event during high dose heparin infusion and resolution of the thrombus in this study. However, there have been occasional reports (4,24,25) of embolic events during regular or low dose heparin therapy after acute myocardial infarction. Larger studies will be necessary to determine whether there is a difference in embolic rate between high and low dose heparin in the treatment of left ventricular thrombus.

Other therapeutic options. For a broad-based left ventricular thrombus without a mobile or protruding component, conservative therapy with oral anticoagulation is usually considered adequate because of the low risk of arterial embolic events (12). Several studies (1–3) have demonstrated that mobile or protruding left ventricular thrombi carry a high embolic risk, reported to range from 22% to 100%. Therefore, a highly mobile thrombus with a prominent protruding segment has been considered to need more intensive medical or surgical therapy, particularly if the thrombus is located on a region of asynergy with a hyperkinetic adjacent wall (3). However, the optimal therapy is controversial, because neither surgical removal nor thrombolytic agents are without major complications or subsequent unfavorable events (8–10,23).

A small proportion of left ventricular thrombi, <20%, have been reported (11,21) to resolve spontaneously after myocardial infarction with or without oral anticoagulant therapy. A systematic prospective investigation of the efficacy of anticoagulation with high dose heparin for resolving left ventricular thrombus has not been reported. Thrombus resolution with oral anticoagulation over several months in small numbers of patients has been described (3,6,7,13,21); however, results were inconsistent. Asinger et al. (13) have reported resolution of six of seven thrombi after oral anticoagulant therapy for 9 ± 5 months. In contrast, Visser et al. (7) have observed that left ventricular thrombus resolved in only 2 of 15 patients over a 4-month period of oral anticoagulation. Nevertheless, oral anticoagulant therapy has been consistently demonstrated to reduce embolic events in patients with left ventricular thrombi, although the incidence of bleeding complications may be as high as 20% on long-term high dose oral anticoagulation (2). For a left ventricular thrombus with a mobile or protruding segment, and thus a high risk for embolization, a treatment that would resolve the thrombus, or at least its risky components, without embolic or hemorrhagic complications would be ideal. This initial resolution of the thrombus could then be followed by treatment with a low dose anticoagulant or a platelet inhibitor, such as aspirin, with a low incidence of bleeding complications.

A previous study (4) from our hospital demonstrated successful resolution of 10 of 16 thrombi with urokinase. Keren et al. (5) later reported two embolic events in four patients treated with streptokinase or urokinase, with a transient neurologic deficit in one patient and stroke followed by death in another. The risks of thrombolytic therapy, hemorrhagic complications and embolic events seem higher than initially assumed (5). Furthermore, thrombolytic therapy must be closely monitored in an intensive care unit, whereas high dose heparin can be initiated on a regular medical ward. The high rate of thrombus resolution with high dose heparin in our study is at least as good as the result of thrombolytic therapy reported by Kremer et al. (4). However, comparisons between studies are hazardous because the age of the thrombus and the underlying heart disease may be different in the two studies. In the previous study (4), successful resolution was dependent on the age of the thrombus: Eight of nine fresh thrombi, which had developed within 4 weeks, were successfully lysed, compared with only two of seven older thrombi. The success rate of thrombolysis appears to depend on the morphology of the thrombi or the underlying heart disease, or both: In the study of Kremer et al. (4), only large thrombi were included, and thrombi located in aneurysms or associated with severe left ventricular dysfunction did not respond well to urokinase. In the present study, we included all mobile or protruding thrombi regardless of size; however, the ages of the thrombi were not known. The proportion of thrombi in aneurysms is lower, only 4 of 23, compared with the study by Kremer et al. (4).

Surgical removal of large, mobile left ventricular thrombi has been performed to reduce the risk of recurrent embolization (9,10). The indications for thrombectomy have differed from one institution to another and remain controversial. If the abnormal myocardial region remains, it may still predispose to new thrombus formation (14). Furthermore, it can be difficult to surgically remove all thrombotic debris, and incomplete removal of thrombotic material may result in embolization at operation. This approach may be indicated in a patient with a large mobile thrombus attached to the wall by a thin stalk. This type of thrombus was seen in only one patient in this

study and was successfully resolved with high dose heparin without any complication. However, the efficacy of high dose heparin compared with surgical removal in this subgroup requires further investigation.

Limitations of the study. This study included a relatively small number of patients, and we were unable to determine the ages of the thrombi. No follow-up was done to detect possible reoccurrence of the thrombus. These aspects need to be addressed in future studies. However, these limitations do not detract from the aim of our study, which was to determine the efficacy and complications of high dose heparin on the initial dissolution of thrombi and complications, such as hemorrhage or embolic events. The high risk of embolic events with mobile or protruding left ventricular thrombi precludes the inclusion of a control group. Low dose heparin was not compared because we have observed embolic events in patients with mobile thrombi during low dose heparin therapy. However, high and low dose heparin treatment should probably be compared in future studies.

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